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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20

Application Number: 09/770,643
Filing Date: January 26, 2001
Appellant(s): TURNER ET AL.

David Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/28/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-3 and 6-8 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Skolnick, J. et al. "From genes to protein structure and function: novel applications of computational approaches in the genomic era" Trends in Biotechnology, vol 18, no. 1 (2000), pp. 34-39.

Bork, P. "Powers and pitfalls in sequence analysis: the 70% hurdle" Genome Research, vol 10 (2000), pp. 398-400.

Doerks T. et al. "Protein annotation: detective work for function prediction" Trends in Genetics, vol 14, no. 6 (1998), pp.248-250.

Smith, TF. et al. "The challenges of genome sequence annotation or "the devil is in the details" Nature Biotechnology, vol 15 (Nov 1997), pp. 1222-1223.

Brenner, S. "Errors in genome annotation" Trends in Genetics, vol 15, no. 4 (April 1999), p. 132.

Bork, P. et al. "Go hunting in sequence databases but watch out for traps" Trends in Genetics, vol 12, no. 10 (Oct 1996), pp. 425-427.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

A. Claims 1-3 and 6-8 are rejected under 35 USC 101 for the reasons already of record on pages 4-6 of the Office Action dated 4/23/02. That Office Action states:

The claimed invention is not supported by a specific and substantial asserted utility, or a well established utility. These claims are directed to an isolated nucleic acid comprising at least 24 contiguous bases of SEQ ID NO:1, nucleic acid molecules which encode the protein of SEQ ID NO:2, and those which hybridize to SEQ ID NO:1, or to the complement thereof. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines (published 1/5/01, 66 FR 1092). The instant application has provided a nucleotide (SEQ ID NO:1) and protein (SEQ ID NO:2) sequence. However, the instant application does not disclose a specific and substantial biological role of the nucleic acid molecule of SEQ ID NO:1, or the protein of SEQ ID NO:2, or their significance, nor any correlation with a specific disease state. Therefore, no specific and substantial utility of these nucleic acid molecules, or protein can be asserted.

It is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. Applicants disclose in the specification that the receptor encoded for by the claimed nucleic acid molecule is believed to encode a protein (termed "NHP" for "novel human protein") related to animal neurexin proteins and contactin-associated proteins (page 1, lines 9-12). However, the basis that the receptor is disclosed in the specification to be homologous to neurexin proteins is not predictive of use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation.

However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polynucleotide of the invention (SEQ ID NO:1) encodes a protein which shares "sequence homology with animal neurexin proteins and contactin-associated proteins." However, this is not a specific and substantial asserted utility, or a well established utility of the protein of the instant specification. No comparisons between the sequence of the protein of the present invention and any neurexin or contactin-associated protein have been disclosed in the specification, nor does the specification disclose that the protein encoded for by the polynucleotide of the present invention has biological activities similar to neurexin and contactin-associated proteins. Sequence homology alone cannot be accepted in the absence of supporting evidence, because the relevant literature acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (Trends in Biotech. 18:34-39, 2000) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (Genome Research 10:398-400, 2000) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (Trends in Genetics 14:248-250, 1998) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (Nature Biotechnology 15:1222-1223, 1997) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. By example, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al. Bone 14:717-720, 1993; see p. 717, second paragraph of Introduction).

Brenner (Trends in Genetics 15:132-133, 1999) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, most homologs must have different molecular and cellular functions. Finally, Bork et al. (Trends in Genetics 12:425-427, 1996) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotide of SEQ ID NO:1, which is only known to encode a protein which shares "sequence homology with animal neurexin proteins and contactin-associated proteins."

Therefore, the instant claims are drawn to a nucleic acid molecule which has a yet undetermined function or biological significance, or correlation to a specific disease state. There is no actual and specific significance which can be attributed to said nucleic acid molecule, or encoded protein, identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, or any significance of the nucleic acid molecule of the present invention, which has not been disclosed in the specification as having any specific or substantial utility, there is no immediately obvious patentable use for them. To employ the nucleic acid molecule of the instant invention to treat, to better understand disease, or to use it to produce a receptor protein to identify substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for the nucleic acid molecule of the invention, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

The Office Action dated 10/22/02 states: Applicants argue that the diagnostic assays described in the specification, which involve polymorphisms are a real-world utility and that, because of this, the present sequences must be useful. Applicants argue that the sequence of the present invention is a "neurexin-like protein" and that neurexins mediate neural processes. Applicants argue that GenBank Accession Nos. NM_130773 and AB077881 are 99% identical to that of SEQ ID NO:1 and 2 of the present invention and that the references cited by the Examiner do not support the lack of utility position made by the Examiner. Finally, Applicants argue that numerous issued patents do not contain examples of

"real-world" utilities. These arguments have been considered, but are not deemed persuasive. First, all issued U.S. patents have a presumption of utility. Second, there are numerous known polymorphisms throughout the DNA and protein databases and that fact that the polynucleotide of the present invention may encode a single nucleotide polymorphism (SNP) is, in itself, neither substantial nor specific since any polynucleotide containing a SNP can be used for diagnostic assays. However, as discussed below and in the Office Action dated 4/23/02, without knowing the functions (i.e. utility) of the polynucleotide and protein of the present invention, one cannot assess a utility for the diagnostic assays using these molecules.

Subsequent references (GenBank NM_130773 and AB077881) by others do teach proteins which are 99% identical to that of the claimed invention. These proteins are named "Caspr" proteins and are members of the neurexin superfamily. Applicants also cite teachings by Zanazzi et al., Bellen et al., Poliak et al., Rios et al. and Spiegel et al. who teach that Caspr proteins are members of the neurexin superfamily and that the functions of these Caspr proteins are well-known. However, it is clear from the references that the neurexin superfamily comprises numerous members belonging to different subfamilies. Caspr is only a member of one of these subfamilies and members of this subfamily have their own specific and substantial functions in neuronal cells which are distinct from other members of the superfamily. While it is known, as Applicants disclose in the specification, that the superfamily of neurexins mediate neuronal processes, the specific neural processes of the proteins and genes of the present invention have not been disclosed. It would not be expected that every subfamily of the neurexin superfamily would have identical functions in the mediation of neuronal processes and that proteins in these individual subfamilies would need to be characterized in order to better understand their specific and substantial role in mediating these processes. Therefore, respectfully, simply stating that the protein of the present invention is related to neurexin and, therefore, mediates neuronal processes is neither substantial nor specific since all neurexins would mediate such general functions. Casprs, for example, appear to associate with myelinated axons and potassium channels (Applicants' specification) and it is the involvement with these functions which confer a specific utility to Caspr proteins. However, Applicants have not provided any specific information regarding the specific utility of the proteins of the present invention which distinguishes them from other members of the neurexin superfamily. Therefore, one of ordinary skill in the art, only knowing that the proteins of the present invention are caspr proteins, which was disclosed subsequent to filing the present application, would still not know what the specific utility of these proteins was, other than the fact that they mediate neuronal processes (Applicants' specification). Therefore, one of ordinary skill in the art would not know how to use a protein, or a gene, which is only

known to generally be involved in neuronal processes, along with potentially hundreds or thousands of proteins.

The references cited by the Examiner were used to show that, in absence of other supporting data, that homology alone is insufficient to determine the function of a protein. Applicants argue that the only function that the protein of the present invention has is that it "mediates neural processes." Again, in itself, this is neither specific, nor substantial since numerous proteins, including G protein-coupled receptors, ion channels, kinases, etc. mediate neural processes. Applicants do argue that the association between neurexins and a variety of neural processes has long been recognized. However, without knowledge of specific functions of the protein of the present invention, one cannot determine that Applicants' invention is useful.

Contrary to Applicants' arguments, the Examiner is not implying that a real-world utility does not require further characterization, only that a patent is not a "hunting license." If Applicants were able to establish that the protein encoded for by the polynucleotide of the present invention was a neurexin protein, or was correlated to a specific disease state, then further characterization would be acceptable. However, Applicants have failed to make this association. Such uses as "for DNA chips" or for chromosome mapping is, again, neither a specific, nor substantial utility since any nucleotide sequence can be used in such an assay. While it is clear that the nucleic acid molecule of the present invention would hybridize to a chromosome, without knowing the function of the protein encoded for by this nucleic acid molecule, then simply identifying that a nucleic acid molecule localizes to a particular region of a chromosome would not provide a use for the nucleic acid molecule of the present invention.

Claim Rejections - 35 USC § 112, first paragraph – enablement

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

Claim Rejections - 35 USC § 101

Applicants argue that the Final Office Action admits that casprs have a specific utility, for example, due to their association with myelinated axons and potassium channels," but that applicants have not provided specific information which distinguishes the proteins of the present invention from other members of the neurexin superfamily. Applicants argue that the protein of the present invention is clearly referred to as a caspr and two subsequent publications teach a protein sharing nearly 100% identity to the protein of the present invention (caspr5). Applicants argue that casprs are distinct members of the neurexin superfamily and caspr2-4 share 42% - 63% homology with each other, whereas the protein of the present invention has 48% - 59% homology to casprs 2-4. Furthermore, casprs share no more than 26% identity to neurexins 1-3. Applicants argue that all that is required for the present invention to possess utility is that it be homologous to known proteins. Applicants cite Example 10 of the Revised Interim Utility Guidelines Training Materials.

These arguments have been considered, but are not deemed persuasive. First, the training example states that the protein in question is 95% homologous to known DNA ligases and only 50% identical to the next closest protein, alpha-actin. However, the function of DNA ligases is well-known and, by definition, all DNA ligases have the same function. Therefore, the function of a protein 95% homologous to known ligases would be clear. In fact, the knowledge that the protein of the invention in the training example was 95% homologous to known DNA ligases was disclosed in the specification. In contrast, the fact that the protein of the present invention was nearly 100% identical to a known caspr5 was not disclosed in the original specification, nor was the protein ever disclosed to be a caspr5. In fact, the identification of the protein of the present invention as a caspr5 was only made based on a subsequent publication. Furthermore, unlike DNA ligases, the function of one caspr cannot be asserted as a function of another caspr because, by Applicants own admission on the record, at least 4 types of casprs are known (caspr2-5). Therefore, in absence of a teaching as to specifically which group of casprs (2-5) the protein of the present invention belongs the artisan cannot determine the specific utility of this protein. Again, unlike DNA ligases, the specific function or utility of one caspr cannot be extrapolated to another caspr.

Applicants have shown post-filing that the protein of the present invention shares only 48-59% homology with other casprs. However, these casprs are of different types (casprs2-4) and the artisan would not be able to determine to which group of casprs the protein of the present invention belonged based on this low homology. Applicants do state that the protein of the present invention is nearly 100% identical to known caspr5. Again, however, the fact that the protein of the invention may be specifically be a caspr5 was not disclosed in the specification as originally filed. The original specification only stated that the protein of the present invention "shares sequence homology with animal neurexin proteins and

contactin-associated proteins." While Applicants have disclosed that the protein of the present invention may be a caspr protein, it was only subsequent to filing that Applicants state that the protein of the present invention is a caspr5, as gathered from subsequent publications. The only information one would gather from the original specification is that the present protein shares homology with the entire family of casprs and neurexins. Applicants have not identified in the specification what specific utility caspr5 has as opposed to the other casprs. In fact, Exhibits P, Q and R of the Appeal Brief only show that the protein of the present invention is homologous to other proteins. No references have been submitted which teach that these proteins in the Exhibits are casprs, as the reference disclosed in these Exhibits only teaches a homology search using the FASTA technique. Even, *arguendo*, these proteins were taught to be caprs2-4, the fact that the protein of the present invention is only 48-59% identical to these is insufficient to assert a utility of the present protein. Again, though the protein of the present invention is nearly 100% identical to caspr5, this was not disclosed in the specification. Therefore, not only have applicants not only taught in the original specification what specific caspr the protein of the invention was, but what utility this protein would possess. "Association with myelinated axons and potassium channels" as taught in the specification, is neither specific nor substantial, as numerous proteins would be expected to "associate" with these and other proteins/cellular structures, especially in the absence of a definition for the vague term "associates."

Applicants further argue that the references cited by the Examiner (Bork, Doerks et al., Smith et al., Brenner, Bork et al.) argue against the position of the Examiner. The Examiner will state that the references as a whole demonstrate that it is difficult to make predictions about function with certainty. Therefore, the fact that the protein has no utility since it lacks 100% consensus on prediction is not the sole basis for the utility rejection, as seen above. Applicants also argue that the Examiner has provided no direct evidence that the protein of the present invention is not a caspr protein. However, based on the relatively low homology to casprs2-4 and the fact that these and caspr5 were only disclosed subsequent to filing and that no specific utility to the protein of the present invention was established, Applicants have not established a *prima facie* case that the protein of the invention is a caspr5 protein with a disclosed, specific or substantial utility. Even, *arguendo*, the artisan may believe the protein of the invention was, generally, a caspr, the artisan would not believe that the protein of the invention was a caspr5 since, again, no characteristics were taught in the disclosure which would convince the artisan that this protein was specifically known to be a caspr5, as opposed to casprs2-4 or other known caspr members.

The argument that the present invention has utility since a SNP at position 812 can lead to an amino acid substitution and that this information can be used in forensic analysis is also not persuasive

since the use of this DNA in forensic analysis is not a utility which is specific for the DNA of the present invention, as any DNA having a polymorphism can be used for this purpose. While the Examiner does understand Applicants' point, the fact that a polymorphism exists is still insufficient to demonstrate utility. Any DNA has the potential for mutation and side-by-side comparison of any DNA can potentially provide forensic information. Furthermore, for example, if two DNA samples were being compared for forensic purposes (i.e. to identify a murderer) and both had the SNP at position 812, then the DNA as a forensic tool would not be useful. This by itself would be inconclusive and would only show that more specific information would be required. This would be of further concern if, for example, as argued by Applicants' these SNPs (such as the one of the present invention) may be present in as much as half of the population.

Applicants argue that the Examiner has been confusing uniqueness and specificity. However, the Examiner is not arguing the specificity of the DNA itself, but rather its use. In other words, while the DNA itself *is* unique, the Examiner is not arguing that the DNA can have no utility since other DNA molecules are already known, but rather that the *use* of this DNA as a probe, or a marker is not a specific use and, therefore, itself is sufficient to demonstrate utility. If this were the case, then anyone can obtain a patent for an isolated strand of DNA by simply asserting that the DNA can be used as a probe, or marker. This, respectfully, is analogous to saying transgenic mice have utility since they can be used as snake food. This would not be a specific utility since nearly every transgenic mouse could be used as snake food.

Applicants further cite *In re Brana*, their major argument being that "further research does not preclude a finding that the invention has utility" and that "further research and development" is (may be) necessary. However, Applicants' reliance on *In re Brana* is misplaced. That court decision determined that a compound which belonged to a family of compounds known to have anti-tumor activity, which is a common and well-established specific and substantial utility for that family of compounds, would be reasonably expected to have anti-tumor activity in light of positive in vitro data with respect to that particular compound since that data has proven to be an indicator of anti-cancer activity by other members of that family. The protein of the instant invention has not been shown in the specification as originally filed to belong to a family of compounds with a common well-established specific and substantial utility. Applicants state that neurexins are associated with mylinated axons and potassium channels. Unlike Brana, Applicants do not provide any in vitro data, or any data correlating to the use of these compounds in vivo. Since the instant specification does not disclose the protein of the present invention as being a member of the neurexin family of proteins, the disclosure that it is only believed to

be a member of this family, which comprises a large number of subfamilies (e.g. caspr 2-5) is not particularly useful.

Furthermore, In re Brana, as stated by Applicants, is concerned mainly with the utility of *pharmaceutical compositions* whereas the present invention is concerned with the utility of receptor *proteins*. Applicants make no mention in their arguments of Brana that the compounds, themselves, to be used in the pharmaceutical compositions do not have utility. Applicants only state that Brana is concerned with the *pharmaceutical compositions* comprising these compounds. Applicants discuss the significance of the FDA and Phase II testing regarding Brana. However, these issues are not relevant in this situation. If Applicants were claiming that the protein of the present invention, or nucleic acids encoding these proteins, could be used in pharmaceutical compositions, that would be analogous. However, the proteins themselves would first need to possess utility in order for the pharmaceutical composition to possess utility. Since the proteins of the present invention do not possess utility, any comparison to Brana is, respectfully, irrelevant. As stated on page 5 of the Office Action dated 4/23/02, a patent is not a hunting license. This same statement can be made with regard to Applicants' argument using *In re Angstadt and Griffin*. Applicants state that "the need for some experimentation does not render the claimed invention unpatentable." However, experimentation only refers to enablement, not utility. No further experimentation should be required. The invention is based on only what is disclosed in the specification. The instant specification is that the protein is believed to be a caspr, with no further support of utility.

Applicants argue that the Examiner dismisses the assertion of 'gene chips' as a utility and argue that only a small number of nucleic acid molecules can be used to track gene expression since only a small number of nucleotide sequences are expressed. They further argue that expression profiling does not require a knowledge of the function of the particular nucleic acid on the gene chip and that the chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular types of tissues. First, what Applicants consider "a small number" includes thousands of nucleotide sequences and the fact that the artisan can determine the level of DNA expression among tissues is not a specific utility as, as previously argued, a large number of DNA molecules can be used for this purpose. The argument regarding "unique" versus "specific" has been addressed above. Furthermore, it is not known what specific and substantial information this determination of tissue levels will provide, given that the function of the encoded protein is not known. In other words, if the function of the encoded protein is not known, then simply determining the expression of this DNA would, by itself, not be useful. It is not known if an increase in this expression is significant, nor whether an increase of decrease in this expression is significant, nor what this alteration represents. For example, no diseases have been linked to

this DNA, let alone its overexpression or underexpression. In addition, the argument that SEQ ID NO:1 can be used to map the 24 coding exons on chromosome 2 is also not persuasive since Applicants did not disclose in the original specification that the DNA encoding the protein of the present invention maps to this location, nor have Applicants identified any disease which map to this locus. All DNA will map to some region on a chromosome. Again, this is neither a specific nor substantial utility of the DNA of the present invention. Using these sequence as specific targets for drug discovery is not substantial. The specification does not characterize the polypeptide encoded by the polynucleotide of the claimed invention. Therefore binding sites, etc. are not identified. Significant further experimentation would be required of the skilled artisan to characterize the protein and search for ligands. There is no disclosure, for example, of how to assay for ligand binding and possible transduction mechanisms, nor is it known which class of drugs to use or what measurements to perform. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not substantial.

Finally, Applicants argue that numerous patents have been issued over the years which do not comply with the new Utility Guidelines. The Examiner states that issued US Patents are presumed to meet all of the requirements for patentability.

Claim Rejections - 35 USC § 112, first paragraph – enablement

Claims 1-3 and 6-8 are rejected under 35 USC 112, first paragraph, for the reasons already of record on page 7 of the Office Action dated 4/23/02 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

ROBERT LANDSMAN
PATENT EXAMINER

Robert Landsman
October 20, 2003

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